

序 言

在不远的过去,生物学、化学和物理学或多或少地被视为相对独立的学科。然而上个世纪后半叶开始,各学科之间的分界变得模糊不清,交叉学科的出现有利于各个学科的发展。之后,数学与计算机科学已成为生物现象建模、模式识别,以及分析像人类基因组项目这类大型数据的必要工具。今天,生命科学领域的任何进展几乎都需要精密的数学方法。对生物系统的刻画已达到前所未有的详细程度,而对生物系统的数学建模正演变成成为实验工作的一个重要组成部分。因此,对经过生物数学训练的研究者的需求正在快速增长。

很多研究机构都曾发起基于数学和生物学界面的训练,其中包括:罗格斯大学、加州大学洛杉矶分校、北卡罗来纳州立大学、犹他州立大学和其他一些学校或研究所。2001年,美国国家研究理事会小组报告提出“系统的本科生物学课程应该包括能启发思维的实验训练和独立从事的研究项目”。为了提高定量的研究技巧,大学教师在生物学的教学过程中应尽可能多的融入数学和物理学知识。该报告称理想的是“将整个课程重新修订”^[1]。随着对跨学科思维方式的训练和解决实际问题的学术课程需求的增强,在生物数学方面开设深入的本科课程已变得较为迫切。2010年数学与生物学展望报告:“本科多学科交融”总结了“迎接挑战:跨生物学、数学和计算机科学的教育”这一项目的结果^[2],并强调如果在高中没有跨学科训练,就应在本科教育第一年开设这样的课程。在《科学》杂志再版并被用于本报告的一篇社论中,作者 Louis Gross 特别强调找到教授入门级定量课程方法的重要性,该方法能使学习生命科学的学生通过一些简单的例子,学会将数学的多个分支而不只是微积分有目的地应用到生物学中^[3]。

你将读到的这本《生物数学进阶》就是因这种独特目的而构思成书。这本书旨在提供数学生物学多样化世界的一个剪影,通过精选的主题和项目令你体验由生物学、数学和计算机科学等多学科交叉形成的惊人进展。配套的实验室手册为当代生物医学研究中一整套现有模型的构造、有效性及改进提供了平台。该教科书旨在展现一些经典概念、最新的和正在进行的科学研究,而不是百科全书式的面面俱到。考虑到适用于生物数学的实用教材或作为一个学期的生物数学介绍课程,本书尽可能写得简明扼要。我们的愿望是你在读完本教程后得到启发,从而走上更为有条不紊的生物数学征途。我们建议大家阅读一些经典教材,如 Murray 的《数学生物学》,从而系统深入地了解该领域。我们也鼓励你更深入地钻研本书介绍的主题,或者学习生物数学的其他课程。

本书分为两大部分。在第一部分,我们阐述了生物数学中的一些经典问题,比如种群增长模型、捕食-被捕食模型、传染病模型和群体遗传学等。尽管这些经典问题在很多地方都有详细的阐述,然而我们的主要目的是介绍一些核心概念和思想,以运用到第二部分的现代热点研究主题中。这些主题可以被包括在任何数学生物学的入门级课程,所以希望这样编排本书可以吸引高等院校的老师教授此类课程。在一个学期的教学中可以涵盖第一部分的所有章节和有选择性地教授第二部分的相关主题。图 1 给出了各章节的关联关系。表 1 列出了在生物学和数学领域内对各章节的简要描述。

凡学过一学期的微积分、普通生物学或统计学的读者都能读懂本书的一至十章。以此为前提,我们认为广大读者完全可以阅读、理解和消化本书。虽然第十一章和第十二章也需要这些预备知识,但透彻理解这两章的内容还需更强的专业知识和学习动机。因此,尽管十一章和十二章是可选章节,但还是鼓励大家根据个人条件和爱好灵活地选择这两章的内容加以深入学习。

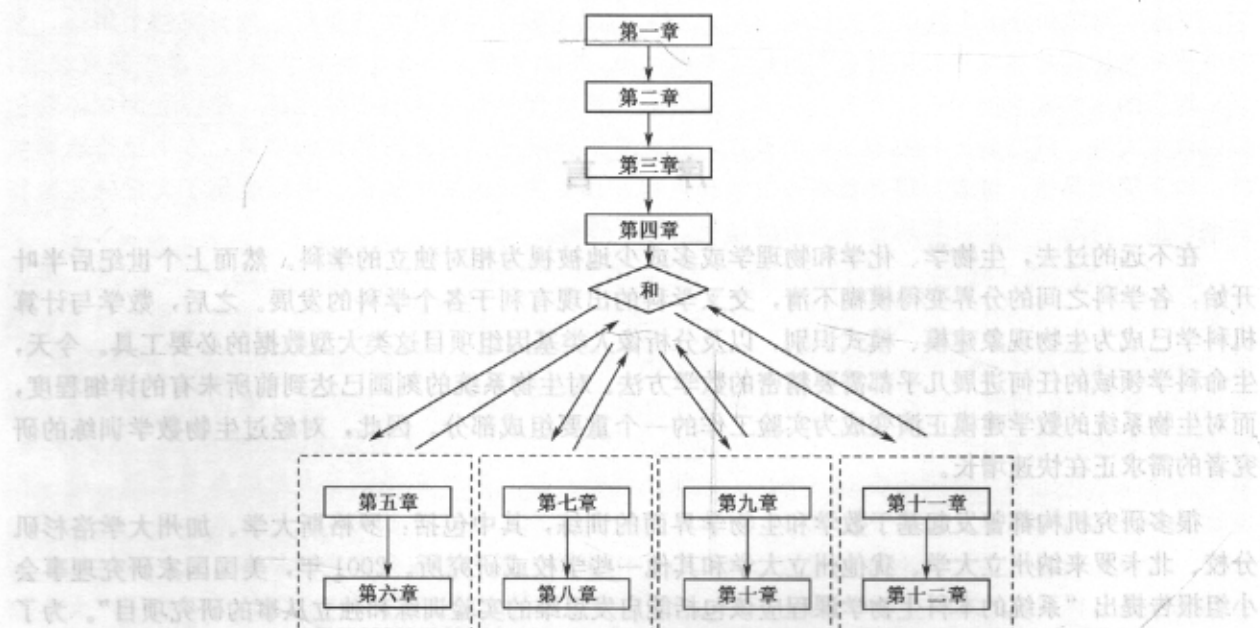


图 1

表 1 各章节涉及的生物和数学主题的从属关系

章节	生物学领域	生物学子领域	数学领域
1	生态学, 保护生物学, 毒理学	种群增长, 收获模型, 药物剂量模型	离散和连续动力系统, 差分方程, 微分方程
2	生态学, 微生物学, 流行病学	流行病模型, 捕食被捕食型, 竞争模型	连续动力系统
3	遗传学	Hardy-Weinberg 法则, 遗传选择, 多基因遗传	离散动力系统, 概率直方图, 正态分布, 中心极限定理
4	遗传学, 生物统计学	遗传可能性	概率分布, 统计学
5	生理学, 内分泌	血糖水平, 葡萄糖动态平衡	数据转换, 风险函数, 统计学
6	生理学, 微生物学	发育学, 细菌感染, 心脏功能, 早产	概率分布, 统计学, 近似值
7	生物化学, 生理学, 细胞生物学	血红蛋白的功能, 协同性, 构象变化	连续动力系统, 概率分布
8	生物化学, 生理学	配体结合	代数方程数值解, 迭代方案, 时间序列
9	内分泌学, 生理学, 细胞生物学	激素搏动	周期变元, FFT, 脉冲检测算法
10	内分泌, 细胞生物学, 分子生物学	荷尔蒙网络	时滞微分方程
11	生理学, 细胞生物学, 分子生物学	生命节律	混杂时间序列, 节律分析
12	生理学, 细胞生物学, 分子生物学	基因芯片, 生物节律的分子生物学	数据正则化, 聚类分析, 时间序列, 节律分析

本书的原则是先介绍生物学问题再引出相应的数学内容, 并且只介绍一些基础的、必要的数学知识。因此书中仅有少量数学定理的证明或一些讨论。数学术语也局限于那些有利于理解、列出公式和解决问题所必要的, 其余则需读者领会。我们感到, 为显示数学和生物学这两种工具在必要时可以相互渗透、融为一体, 我们应该避免可能出现的一般化诉求 (这是一种在理论数学环境中受过训练者其近乎天性的诉求)。经过深思熟虑, 我们选择不去过多地探究源于某些主题和项目的数学奥妙, 对希望本书可以涵盖这些内容的读者, 我们深表歉意。

感谢我们在 Sweet Briar 学院和弗吉尼亚大学的所有学生, 特别要感谢那些在本教材及实验手册编写

和课堂教学过程中提供有益意见的同学: Jennifer McDonaugh, Jamie Jensen 和 Suzanne Harvey。感谢为我们所选章节和实验项目提供反馈意见的同事: Marc Breton, Jeff Graham, Stan Grove, David Housman, Eric Marland, Pamela Ryan, Philip Ryan, Karen Ricciardi 和 Bonnie Schulman 博士, 并感谢 Anna Kovatcheva 为我们收集了第四章练习一的数据。Stefan Robev 和 Ryan King 博士仔细地校对了初稿, Jane Carlson 协助做了早期的编辑工作, 在此一并致谢。我们衷心感谢 Academic Press/Elsevier 出版社的编辑为本书出版付出的辛勤劳动, 他们是 Chuck Crumley, David Cella, Kelly Son-nack, Nancy Maragioglio, Luna Han 和 Sally Cheney。Tom Loftus 为规范语言和最终定稿付出了大量的心血, 谨此表示由衷的感谢。最后, 我们要感谢美国国家科学基金的本科教育奖项 0126740 和 0304930 的支持, 美国国家卫生研究所的 NIDDK 奖项 R25 DK064122、R01 DK51562 和 R25 DK064122 的支持。

现在, 就请你翻开这本书, 开始探索生物数学的新旅程吧。

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(翻译: 唐五一, 肖燕妮
审校: 陈兰林)

PREFACE

In the not so distant past, the sciences of biology, chemistry, and physics were seen as more or less separate disciplines. Within the last half-century, however, the lines between the sciences have become blurred, to the benefit of each. Somewhat more recently, the methods of mathematics and computer science have emerged as necessary tools to model biological phenomena, understand patterns, and crunch huge amounts of data such as those generated by the human genome project. Today, virtually any advance in the life sciences requires a sophisticated mathematical approach. Characterization of biological systems has reached an unparalleled level of detail, and modeling of biological systems is evolving into an important partner of experimental work. As a result, there is a rapidly increasing demand for people with training in the field of biomathematics.

Training at the interface of mathematics and biology has been initiated in a number of institutions, including Rutgers University, the University of California at Los Angeles, North Carolina State University, the University of Utah, and many others. In 2001, a National Research Council panel found that "undergraduate biology education needs a more rigorous curriculum including thought provoking lab exercises and independent research projects." To improve quantitative skills, faculty members should include more concepts from mathematics and the physical sciences in biology classes. Ideally, the report says, "the entire curriculum would be revamped."¹ As the demand for academic programs that facilitate interdisciplinary ways of thinking and problem solving grows, many of the challenges for creating strong undergraduate programs in mathematical biology have become apparent. The report *Math & Bio 2010: Linking Undergraduate Disciplines* summarizes the results of the project *Meeting the Challenges: Education Across the Biological, Mathematical, and Computer Sciences*² and emphasizes that interdisciplinary programs should begin as early as the first year of college education, if not in high school. In one of the articles, an editorial reprinted from the journal *Science* and used in the report, the author Louis Gross specifically underscores the importance of finding ways to "teach entry-level quantitative courses that entice life science students through meaningful applications of diverse mathematics to biology, not just calculus, with a few simple biological examples."³

The book that you are about to read, our *An Invitation to Biomathematics*, was conceived and written with this exact goal in mind. This book is meant to provide a glimpse into the diverse world of mathematical biology and to invite you to experience, through a selection of topics and projects, the fascinating advancements made

possible by the union of biology, mathematics, and computer science. The laboratory manual component of the text provides venues for hands-on exploration of the ever-present cycle of model development, model validation, and model refinement that is inherent in contemporary biomedical research. The textbook aims to provide exposure to some classical concepts, as well as new and ongoing research, and is not meant to be encyclopedic. We have tried to keep this volume relatively small, as we see this text used as a first reading in biomathematics, or as a textbook for a one-semester introductory course in mathematical biology. It is our hope that after reading this *Invitation* you will be inspired to embark on a more structured biomathematical journey. We suggest considering a classical textbook, such as Murray's *Mathematical Biology*, to gain a systematic introduction to the field in general. We also encourage you to delve deeper into some of the more specialized topics that we have introduced, or to take additional courses in mathematical biology.

The textbook is divided into two parts. In Part I, we present some classical problems, such as population growth, predator-prey interactions, epidemic models, and population genetics. While these have been examined in many places, our main purpose is to introduce some core concepts and ideas in order to apply them to topics of modern research presented in Part II. Because we also felt that these topics are likely to be covered in any entry-level course in mathematical biology, we hope that this organization will appeal to college and university faculty teaching such courses. A possible scenario for a one-semester course will be to cover all topics from Part I with a choice of selected topics from Part II that is, essentially, modular in nature. The diagram in Figure 1 outlines the chapter connectivity. Table 1 presents brief chapter descriptions by biological and mathematical affiliation.

A committed reader who has had the equivalent of one semester-long course in each of the disciplines of calculus, general biology, and statistics should be able to follow Chapters 1 to 10. With these prerequisites, we believe that the book can be read, understood, and appreciated by a wide audience of readers. Although Chapters 11 and 12 also comply with those general prerequisites, a quality understanding of the fundamental concepts covered there may require a somewhat higher level of general academic maturity and motivation. Thus, although Chapters 11 and 12 can be considered optional in essence, we would like to encourage the readers to explore them to the extent and level of detail determined by their individual comfort level.

Our rule while writing this book was that the biology problem should lead the mathematics, and that we only present the mathematics on a need-to-know basis and in the amount and level of rigor necessary.

As a consequence, very few mathematical theorems are proved or even discussed in the text. We limited ourselves to the minimal

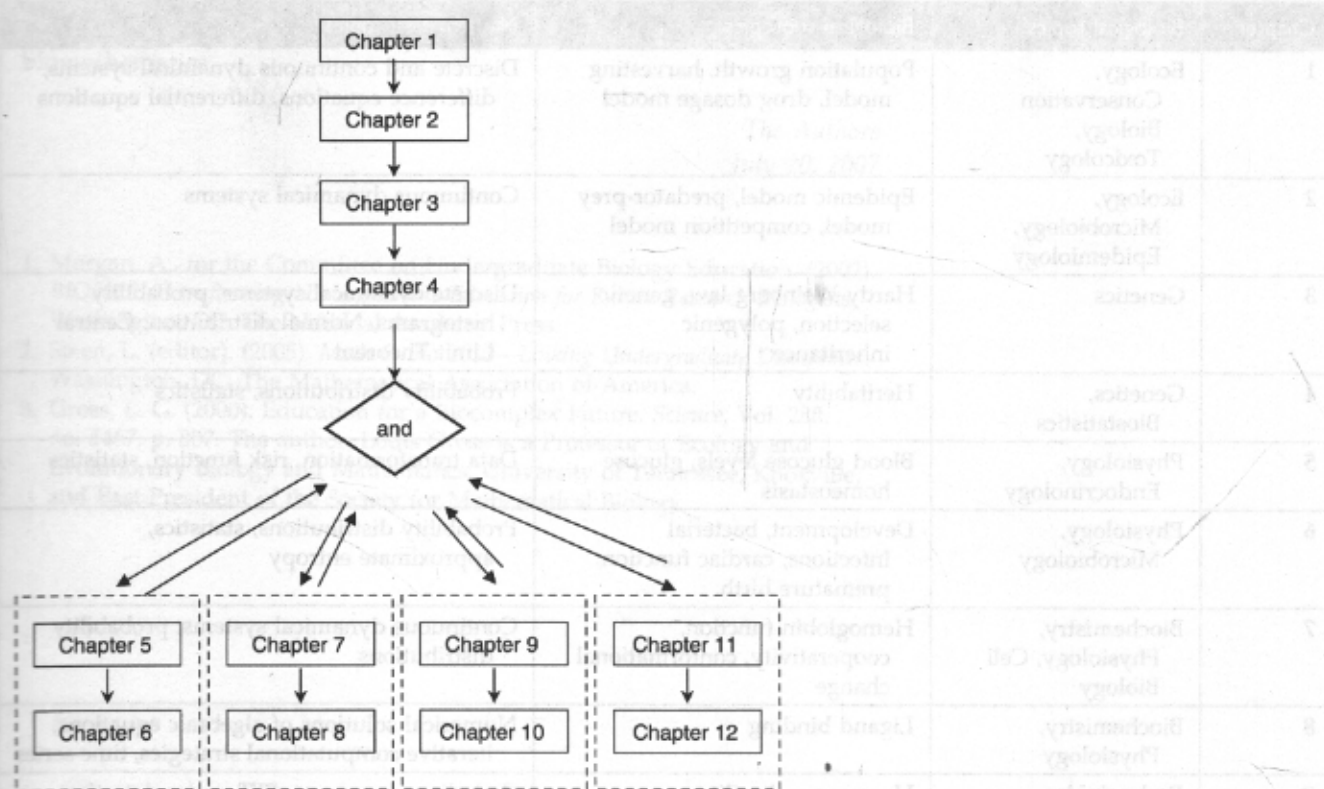


FIGURE 1.

mathematical terminology necessary for understanding, formulating, and solving the problem, relying on the reader's intuition for the rest. We felt that in the interest of showing how the tools of mathematics and biology can blend together and work as one when needed, we should resist the urge for possible generalizations (an urge that is almost second nature for those of us trained in the field of theoretical mathematics). The choice not to explore many of the possible exciting mathematical venues that stem from some of the topics and projects was deliberate, and we apologize to those readers who wish we had included them.

We would like to thank all of our students at Sweet Briar College and the University of Virginia, especially Jennifer McDonough, Jamie Jensen, and Suzanne Harvey, for providing valuable comments and opinion throughout the development and classroom testing of the textbook and laboratory manual manuscripts. We also thank our colleagues Drs. Marc Breton, Jeff Graham, Stan Grove, David Housman, Eric Marland, Pamela Ryan, Philip Ryan, Karen Ricciardi, and Bonnie Schulman for their feedback on selected chapters and/or laboratory projects, and Anna Kovatcheva for collecting the data used in Exercise 1 of Chapter 4. We appreciate the help of Dr. Stefan Robev and of Ryan King, who carefully proofread the entire first draft of the manuscript, and of Jane Carlson, who assisted with its early technical editing. We are also indebted to all

Chapter	Biological topics	Biological subtopics	Mathematical topics
1	Ecology, Conservation Biology, Toxicology	Population growth, harvesting model, drug dosage model	Discrete and continuous dynamical systems, difference equations, differential equations
2	Ecology, Microbiology, Epidemiology	Epidemic model, predator-prey model, competition model	Continuous dynamical systems
3	Genetics	Hardy-Weinberg law, genetic selection, polygenic inheritance	Discrete dynamical systems, probability histograms, Normal distribution, Central Limit Theorem
4	Genetics, Biostatistics	Heritability	Probability distributions, statistics
5	Physiology, Endocrinology	Blood glucose levels, glucose homeostasis	Data transformation, risk function, statistics
6	Physiology, Microbiology	Development, bacterial infections, cardiac function, premature birth	Probability distributions, statistics, approximate entropy
7	Biochemistry, Physiology, Cell Biology	Hemoglobin function, cooperativity, conformational change	Continuous dynamical systems, probability distributions
8	Biochemistry, Physiology	Ligand binding	Numerical solutions of algebraic equations, iterative computational strategies, time series
9	Endocrinology, Physiology, Cell Biology	Hormone pulsatility	Periodic components, FFT, pulse-detection algorithms
10	Endocrinology, Physiology, Cell Biology	Hormone networks	Continuous dynamical systems with delays
11	Physiology, Cell Biology, Molecular Biology	Circadian rhythms	Confounded time series, rhythm analysis
12	Physiology, Cell Biology, Molecular Biology	Gene chips, molecular biology of circadian rhythms	Data normalization, clustering strategies, time series, rhythm analysis

TABLE I.
Chapter topics by biological and mathematical affiliation

of our editors at Academic Press/Elsevier: Chuck Crumley, David Cell, Kelly Sonnack, Nancy Maragioglio, Luna Han, and Sally Cheney, for their encouragement and assistance throughout. Our deep gratitude goes to Tom Loftus who put many hours into editing the final draft of the manuscript for style and language consistency. Finally, we appreciate the support of the National Science Foundation under the Department of Undergraduate Education awards 0126740 and 0304931, and the support of the National Institutes of Health under NIDDK awards R25 DK064122, R01 DK51562, and R25 DK064122.

You are now invited to turn the page and begin your exploration of biomathematics.

The Authors

July 20, 2007

1. Morgan, A., for the Committee on Undergraduate Biology Education. (2002). *BIO2010: Transforming Undergraduate Education for Future Research Biologists*. Washington, DC: The National Academy Press.
2. Steen, L. (editor). (2005). *Math & Bio 2010—Linking Undergraduate Disciplines*. Washington, DC: The Mathematical Association of America.
3. Gross, L. G. (2000). Education for a Biocomplex Future. *Science*, Vol. 288, no. 5467, p. 807. The author, Louis Gross is a Professor of Ecology and Evolutionary Biology and Mathematics, University of Tennessee, Knoxville, and Past-President of the Society for Mathematical Biology.

PROCESSES THAT CHANGE WITH TIME: INTRODUCTION TO DYNAMICAL SYSTEMS

Using Data to Formulate a Model

Discrete Versus Continuous Models

A Continuous Population Growth Model

The Logistic Model

An Alternative Derivation of the Logistic Model

Long-Term Behavior and Equilibrium States

Analysing Equilibrium States

The Logistic Model for Discrete Population Growth

A Population Growth Model with Delay

Modeling Physiological Mechanisms of Drug Elimination

Using Computer Software for Solving the Models

Some BIOLOGICAL APPLICATIONS

Appendix: Solving Laboratory Exercises for Chapter 1

mathematical representation of reality uses mathematics to describe a phenomenon of nature. There are many mathematical tools that can be used in this process, including statistics, calculus, probability, and differential equations. Different methods may provide insights to different aspects of the problem, and there is often much debate about what approach is preferable. Mathematical models that represent reality are the subject of this text.

Building a good mathematical model is a challenging task that requires a solid understanding of the nature of the system being modeled, as well as the mathematical tools being used to describe it. Because mathematical models are quite diverse, it is difficult to specify a process that would apply to all problems. However, there are fundamental principles that facilitate and guide the creative process. They are:

1. Initially, a model should be simple.
2. It is crucial to test the model under as many conditions as reasonable.
3. If the model seems to be successful in some ways but fails in others, try to modify the model rather than starting over.

In this chapter, we discuss how biological models of one variable change over time. The first model we study is growth of a population. Our initial attempt is based on numerical data. Later, we build the model based on conjectures about "how populations should grow." Both models yield essentially the same result, and although these constructions are successful in the short term, both are flawed because the long-term behavior they predict is